Towards the Absolute Quantitation of DCE-MRI Pharmacokinetic Parameters: Addressing the Assumption of Constant Contrast Reagent Relaxivity and its Effect on K^{trans}

G. Metzger[1,2], D. Thomasson[3], M. Bernardo[4,5], P. Choyke[5]

[1]Philips Medical Systems, Bethesda, MD, United States, [2]Center for Magnetic Resonance Research, University of Minnesota, Minneapolis, MN, United States, [3]National Institutes of Health, Clinical Center, Bethesda, MD, United States, [4]SAIC, Frederick, MD, United States, [5]Molecular Imaging Program, National Cancer Institute, Bethesda, MD, United States

INTRODUCTION: The characterization of dynamic contrast enhanced MRI (DCE-MRI) is a topic of ongoing research as models to explain both the physiologic and magnetic resonance phenomena are developed, simulated and experimentally tested. The ultimate goal is to achieve absolute quantitation of physiologically meaningful parameters. Achieving this goal would allow comparison of studies intra and inter individually for following current and evaluating new therapies.

Because of the limited amount of data acquired in a typical DCE-MRI study, many assumptions are necessary to make estimates of pharmacokinetic parameters. Methods to preclude a specific assumption should be addressed by weighing its impact on parameter estimation verses the need for additional assumptions and the necessity for acquiring additional data. All studies to date which attempt to obtain concentrations for quantitation through kinetic analysis assume a constant contrast reagent relaxivity. Meanwhile, previous work has demonstrated the effect of local macromolecular content (MMC) on relaxivity [1] and related magnetization transfer studies to macromolecular proton fractions [2] which when combined allows the variable relaxivity *in vivo* to be addressed [3-4]. The significance of determining tissue dependent relaxivity as opposed to assuming a constant relaxivity is demonstrated in this work by focusing on K^{trans} when estimating pharmacokinetic parameters with a General Kinetic Model.

METHODS: Data from 4 patients were analyzed for this comparison. Imaging was performed on a 3 Tesla Philips Intera scanner (Philips Medical System**,** Best, The Netherlands) with combined SENSE cardiac coil and an endorectal coil (BPX-15, Medrad, Indianola, PA) tuned to 127.8 MHz. After a digital rectal examination, the endorectal coil was inserted and inflated with a fluorinated liquid to a volume of approximately 60 ml. DCE-MRI data were acquired during a single dose injection of Gd-DTPA (Magnevist; Berlex Laboratories, Wayne, NJ) at a rate of 3 ml/sec with an injector (Spectrix MR Injection System; Medrad, Pittsburg, PA) . The DCE-MRI sequence was a 10 slice 3D T1W fast field echo (FFE) acquisition with a temporal resolution of 3.1 sec, TR/TE of 5.5/2.1 ms, 15 degree flip angle, 26 cm FOV, effective SENSE factor of 2 and a resolution of 0.86x1.18x6.0mm. The 3D FFE MT sequence was acquired with and without an off-resonance saturation pulse and 220 mm FOV, TR/TE 116/3.7 ms and flip angle 18 ^{o} with a final acquired resolution of 1.72 x 1.72 x 6 mm. A pre-contrast T1 map was calculated with a two flip angle approach by acquiring an identical 3D acquisition to that of the DCE-MRI with a flip angle of 5 degrees to use along with the pre-contrast data from the dynamic acquisition.

A General Kinetic Model (GKM) was implemented in the Philips PRIDE environment allowing parameter estimation with either the assumption of constant relaxivity or the use of calculated relaxivity correction maps based on the subjects' MTR data. The relationship of MTR to relaxivity was determined to be linear in previous phantom studies with an intercept of 5.0 mM/sec and slope of 0.07 (mM/sec/MTR) [3]. GKM analysis produced estimates of the parameters K^{trans} (volume transfer constant, min^{-1}), k_{ep} (flux rate constant between extravascular-extracellular space (EES) and plasma, min^{-1}) and ve (the volume of EES per unit volume of tissue). The focus of this study will be on K^{trans} as it is the only estimated parameter in this model affected by the intensity of the signal enhancement curves.

RESULTS: The percent decrease in Gd-DTPA concentration, [Gd], as a function of MTR is shown in Figure 1. The average decrease in [Gd] when taking into account MMC modified relaxivity is 22.9% with an average MTR of 21.3%. A representative set of data from patient 1 is shown in figure 2. The native T2W image and MTR map from the same slice are displayed along with the K^{trans} maps generated without Ktrans(noMT) and with Ktrans(MT) relaxivity correction maps. The overestimation of [Gd] when assuming a constant relaxivity can be observed in Ktrans(noMT) where the arrow shows higher estimates of Ktrans than the calculations accounting for MMC adjusted relaxivity, Ktrans(MT). The average K^{trans} values over regions of the parametric maps showing rapid enhancement were compared with and without MT correction. Table 1 compares the average K^{trans} values over these ROIs along with the averaged MT ratios. A paired two sample for means t-Test showed significant differences between the Ktrans(MT) and Ktrans(noMT) data (P = 0.006).

DISCUSSION: There is an overestimation of K^{trans} when assuming constant relaxivity. If DCE-MRI data is to be used to follow or evaluate treatments it would make sense that we would want to decouple changes of relaxivity from changes in the pharmacokinetic parameters we are attempting to estimate. Additional assumptions are made when using phantom data to characterize the effect of MMC on relaxivity as was done to obtain the relationship in figure 1. Further investigation is required to determine if these assumptions are valid.

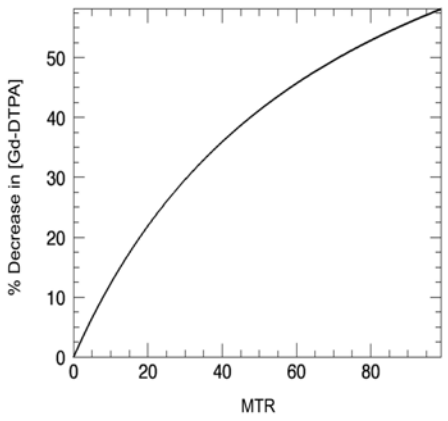

Figure 1: Percent decrease of [Gd] as a function of MTR given by the relation (5 + 0.07*MTR).

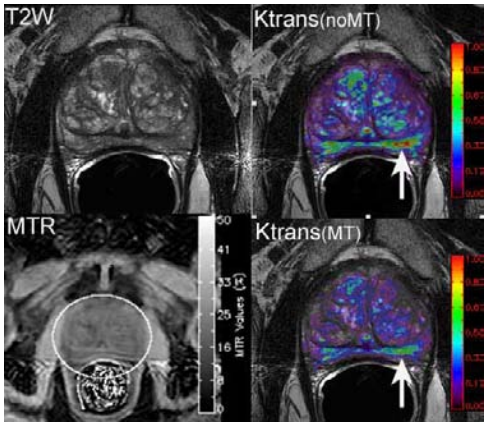

Figure 2: T2W and MTR images from patient 1. Ktrans maps overlayed on the T2W images show the overestimation of Ktrans with noMT verses MT as denoted by the arrow.

Patient	Ktrans MT	Ktrans noMT	MTR (%)
1	0.67 (0.16)	0.87 (0.21)	21.25 (1.51)
2	0.60 (0.21)	0.73 (0.23)	22.05 (1.03)
3	0.71 (0.14)	0.97 (0.19)	25.69 (0.98)
4	0.45 (0.21)	0.57 (0.27)	20.12 (1.25)

Table 1: Average K^{trans} and MTR values from ROIs of rapid enhancement. Standard deviations are in (). Units for K^{trans} are min^{-1}.

1) Greg J. Stanisz, R. Mark Henkelman, MRM 44:665–667 (2000)
2) Davies GR, Ramani A, Dalton CM, Tozer DJ, Wheeler-Kingshott CA, Barker GJ, Thompson AJ, Miller DH, Tofts PS., Mult Scler. 2003 Jun;9(3):246-9.
3) Thomasson D, Bernardo M, Srikanchana A, Metzger G, Swaminathan S, Choyke P, Gharib A., RSNA Abstract, Chicago, 2004.
4) Thomasson D., Metzger G., Swaminathan S,. Bernardo M. Choyke P., Gharib A., Li K, ISMRM Abstract, Miami, 2005.